Strengths and Weaknesses of HIV Protease Inhibitor Therapy

Bierman, W.F.W.

2010

document version
Publisher's PDF, also known as Version of record

SUMMARY

About 30 years ago the scientific world became aware of a new disease that was killing young homosexual men. This disease was characterized by an acquired immune deficiency disorder (AIDS). It was soon discovered that AIDS was caused by the human immunodeficiency virus (HIV). Fifteen years later extensive research had led to a treatment consisting of a combination of 3 or more drugs with the capacity to lastingly suppress the virus. Thus it became possible to restore a terminally impaired immune system.

The group of HIV protease inhibitors (PI) is one of the cornerstones of combination antiretroviral therapy (cART). One of the first PIs, ritonavir, is currently rarely used full-dose because of its side effects. However, adding a low-dose of ritonavir to another PI was found to substantially increase the efficacy of the latter PI. These so-called ritonavir-boosted PIs belong to the most potent anti-HIV drugs currently available. **Chapter one** provides an overview of the strengths and weaknesses of this class of anti-HIV drugs. In the subsequent chapters of this thesis several of these strengths and weaknesses are studied in further detail.

Strengths

Chapter two addresses the potency of PIs. The main problem of treating HIV/AIDS in the early days was the ability of the virus to easily gain resistance to any single drug therapy by way of rapid viral mutations. As more drugs were introduced onto the market, therapies involving the combining of multiple drugs became a possibility. Multiple anti-HIV drugs when used in tandem proved effective in blocking the ability of the virus to escape therapy by mutation. However, combination therapy carries some disadvantages such as the combined side effects of the different drugs. Furthermore, clinical practice with ritonavir-boosted PIs showed that the occurrence of resistance mutations was extremely rare if the patients had never before been treated with anti-HIV drugs. This observation, together with reservations acknowledging the challenges of combination therapy, led to the question whether HIV could be treated with ritonavir-boosted PIs only (monotherapy).

In **Chapter two** we review all studies that examined whether HIV could be treated with monotherapy with PIs. We found that, compared to cART, ritonavir-boosted PI monotherapy is less effective. This difference in efficacy is statistically significant, but it is not very large. In fact, most of the patients (~70%) did well on monotherapy. Moreover, most patients who experienced virological failure during monotherapy were able to respond successfully to subsequent supplemental combination therapy with two other drugs: the so-called nucleoside reverse transcriptase inhibitor (NRTI)-backbone. Therefore it is possible that certain patients would benefit from PI monotherapy. We call this the '3-1-3 strategy': starting with cART (induction); once HIV is suppressed, simplifying to PI monotherapy (maintenance); and re-initiating the NRTI-backbone in the case of reappearance of the virus in the blood (re-induction). The immediate

advantages of this novel treatment strategy may be the reduction of long-term side effects, costs, and NRTI-resistance. The '3-1-3 strategy' is being studied presently.

Weaknesses

In **Chapters three through six** explanations are sought for those patients in whom treatment with PIs fails to suppress or fails to sustain the suppression of the virus. In **Chapter three** we describe three patients whose virus is not suppressed despite the use of the ritonavir-boosted PI lopinavir/ritonavir. In the viruses of these three patients, two mutations were detected which hitherto had not been known as resistance-related mutations. Remarkably, these two mutations were sufficient for causing resistance to lopinavir/ritonavir. It was previously assumed that at least five protease mutations were necessary for resistance to lopinavir/ritonavir. Subsequently, the mutations found have been added to the international list of known resistance mutations.

In **Chapters four and five** we examined whether the efficacy of PIs might be reduced by unique characteristics of patient physiology rather than those characteristics intrinsic to the virus. In **Chapter four** we investigated whether the PIs atazanavir, lopinavir and ritonavir can be transported by any of 11 efflux pumps (ABC transporters). These pumps are located on various cells in the body and are able to pump toxic substances out of the cell. For example, due to the presence of these efflux pumps in endothelial cells in the central nervous system, many drugs cannot penetrate the brain (the so-called blood-brain barrier). In the field of oncology it is known that cancer cells can be resistant to chemotherapy because they are able to efflux anti-cancer drugs by ABC transporters.

The experiments described in **Chapter four** show that atazanavir, lopinavir and ritonavir are not efficiently transported by any of the 11 ABC transporters. It is therefore unlikely that efflux pumps play a role in the failure of PI therapy. A number of pumps, however, can be substantially blocked by the tested PIs. As a result other substances can not be transported by these pumps. Thus it is possible that side effects of concomitantly used drugs, that can normally be transported, are strengthened. It is also possible that certain important metabolic functions of the pumps are hindered inadvertently leading to adverse events.

In **Chapter five** we describe how T cells, the main target cells of HIV, were continuously exposed to increasing concentrations of atazanavir, lopinavir and ritonavir. The purpose of the experiments was to provoke adaptation of these cells to the PI (cellular resistance) and then see if this change would lead to decreased anti-HIV effects of the PI (viral resistance).

We found that only cells that were exposed to lopinavir became moderately resistant to the PI. This cellular resistance was not caused by increased expression of efflux pumps. Furthermore, the intracellular concentration of lopinavir was unchanged compared to the original, untreated cells. However, in the resistant cells we found evidence of decreased programmed cell death (apoptosis). It is not known whether

these in vitro findings also occur in vivo in the T cells of patients receiving prolonged treatment with lopinavir.

Chapter six deals with one of the main side effects of most PIs: an increase in serum levels of cholesterol and triglycerides (fatty acids). This side effect is sometimes a reason for replacing the PI with an alternative drug. Despite several studies it is still not clear whether the percentage of lipid increase is directly related to the concentration of PIs in the blood. If such a relationship would exist, reducing the dosage of the PI might improve the lipid concentrations. Previous studies contradict each other. In two patient groups we investigated the relationship between the concentration of lopinavir and lipid increase: the patients of the HIV outpatient clinic of the VU University Medical Center that were treated with lopinavir and patients who took part in a study comparing the effects of two different HIV treatment combinations including lopinavir. In both groups there was no correlation found between lopinavir concentration and the increase of cholesterol and triglycerides.

Conclusion

In **Chapter seven** the pros and cons of treatment with ritonavir-boosted PIs are weighed using a 'Strengths, Weaknesses, Opportunities and Threats (SWOT) analysis'.

The main advantages of ritonavir-boosted PIs are the high probability of inducing an enduring complete suppression of HIV and the very low mutation rate in the case of therapy failure. The potency of the PIs is underlined by their being the only class of anti-HIV drugs effective as monotherapy. In contrast, specific side effects such as lipid and vascular changes may be harmful in the long term. Unfortunately, it seems not possible to moderate PI-induced lipid changes by dose reduction. Furthermore, our experiments with ABC transporters and T cells indicate that prolonged use of PIs could have unexpected side effects. Additionally, the virus is not sustainably suppressed in some patients without the emergence of resistance mutations. The new mutations that we have found only partly explain this phenomenon.

This leads to the conclusion that ritonavir-boosted PIs deserve an important role in the future of HIV treatments, but that the choice of drugs should be made on an individual patient basis. In the resource-limited settings of poorer countries relatively few patients are being treated with PIs, but in coming years we expect an increasing demand for the prescription of ritonavir-boosted PIs. Especially in these countries, the abovementioned 3-1-3 strategy might assume large proportions. Importantly, this only seems justified in the presence of facilities that assure proper monitoring of the HIV treatment.